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C_2-Symmetric Bissulfoximines as Ligands in Copper-Catalyzed Enantioselective Diels–Alder Reactions

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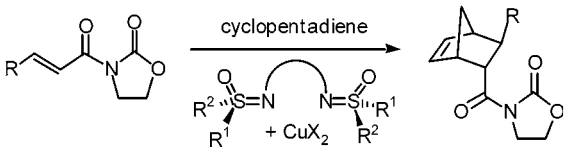
ABSTRACT



Bissulfoximines have been used as chiral ligands in copper-catalyzed enantioselective Diels–Alder reactions between acryloyl-2-oxazolidinones and cyclopentadiene. After optimizing the ligand structure, the metal source, the counterions, and the solvent, products with up to 93% ee have been obtained.

Over the past decades, asymmetric metal catalysis has become a major area in organic chemistry.[1] In this context, it is particularly important to search for new compounds, which can serve as chiral ligands, and to explore their applicability in the synthesis of optically active compounds. For several years, we[2] and others[3] have been involved in the investigation of sulfoximines[4] with the intention to use their metal-binding properties[5] in the development of new chiral catalysts. Along these lines, C_2-symmetric bissulfoximines have recently been introduced,[3,6] which led to products with very high enantiomeric excesses in allylic alkylations[7] and hetero-Diels−Alder reactions,[8] catalyzed by palladium and copper complexes, respectively. To extend the comparison of catalysts bearing these new bissulfoximines with those having well-established ligands[9] such as bisoxazolines[10] and semicorrines,[11] we investigated the [4+2]-cycloaddition between cyclopentadiene (**1**) and acryloyl-2-oxazolidinones **2** (Scheme 1).[12] Various bissulfoximines **4** and **5** with

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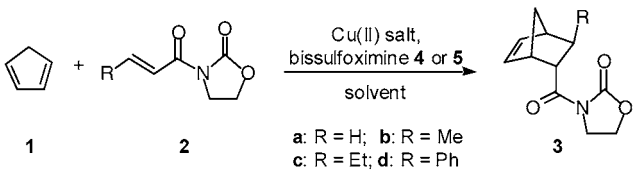
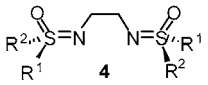
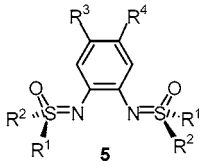
Scheme 1





	R^1	R^2
4a:	Me	Ph
4b:	*i*-Pr	Ph
4c:	*c*-Pent	Ph
4d:	Me	Biph
4e:	Me	3,5-di-*t*-Bu-Ph
4f:	2-MeO-Ph	Me
4g:	2-MeO-Naph	Me



	R^1	R^2	R^3	R^4
5a:	Me	Ph	H	H
5b:	2-MeO-Ph	Me	H	H
5c:	Me	Ph	NO_2	H
5d:	Me	Ph	F	F
5e:	Me	Ph	Me	Me

ethylene and arenes as bridging units, respectively, were screened and evaluated on their ability to give enantioselective copper catalysts. At this early stage, all reactions were performed in dichloromethane as the solvent, using **2a** as dienophile and $Cu(OTf)_2$ as the copper source.

First, the use of the ethylene-bridged bissulfoximines **4** was investigated. With 10 mol % of a catalyst prepared from a 1:1 mixture of bissulfoximine **4a** and $Cu(OTf)_2$, **3a** was obtained in excellent yield (98%) having an enantiomeric excess (ee) of 66% (Table 1, entry 1). The endo-isomer dominated with a selectivity of 93:7. Increasing the steric demand of the aliphatic substituent R^1 of the bissulfoximine by changing the methyl to an isopropyl or a cyclopentyl group reduced the enantioselectivity in the product formation (49 and 15% ee, respectively) without affecting the endo/exo ratio (entries 2 and 3). Modifying the aryl substituent R^2 had only a minor effect, except when a 2-methoxy group was introduced (entries 6−9). In these cases the ee increased and reached a maximum of 83% (entry 7). Generally, lowering the reaction temperature had a beneficial effect on the enantioselectivity (entries 7 and 9 versus 6 and 8).

The importance of the 2-methoxy substituent was also observed when aryl-bridged bissulfoximines **5** were used as ligands. Here, the ee of **3a** was slightly higher in the catalysis with **5b** than with **5a** (entries 10 and 11). To determine the influence of electronic properties of the ligand, bissulfoximines **5c**−**e** were synthesized, and their catalytic properties were compared to those of **5a** and **5b**. Obviously, electron-withdrawing substituents such as nitro or fluoro groups in the 4 (R^3) and 5 (R^4) positions of the bissulfoximine arene backbone reduced the enantioselectivity in the formation of **3a** (entries 12 and 13). Electron-donating methyl groups, however, had a positive effect (entry 14) on the ee of **3a**.

Uniformly, *S*,*S*-bissulfoximines **4** and **5** afforded the bicyclic product **3a** with 2*R* configuration, whereas (*R*,*R*)-**4** and (*R*,*R*)-**5** gave (2*S*)-**3a**. A test reaction with **2b** as substrate and a $Cu(OTf)_2$ catalyst bearing **4f** as ligand afforded the corresponding endo-product with 84% ee.[13]

Next, we turned our attention to the applicability of other metal salts[14] and found that the enantioselectivity was significantly affected by the nature of the counterion (Table 2).[15] Whereas copper dichloride and copper bistrifluoroacetate were unselective catalysts (Table 2, entries 2 and 3), less coordinating counterions proved to be more suitable, and among all those tested, copper(II) perchlorate led to the best results with respect to product ee. Thus, with bissulfoximine **5a**[16] as ligand the ee of **3a** could be raised from

Table 1. Influence of the Ligand Structure on the Diels−Alder Reaction[a]

entry	bissulfoximine	yield of **3a** (%)	ee of **3a** (%)[b]	endo/exo[c]
1	**4a**	98	66	93:7
2	**4b**	98	49	93:7
3	**4c**	98	15	93:7
4	**4d**	94	64	88:12
5	**4e**	98	59	87:13
6	**4f**	98	76	93:7
7[d]	**4f**	98	83	94:6
8	**4g**	98	76	91:9
9[d]	**4g**	98	80	88:12
10	**5a**	98	75	93:7
11	**5b**	98	79	91:9
12	**5c**	98	59	90:10
13	**5d**	98	72	93:7
14	**5e**	98	81	93:7

[a] Reaction conditions: **1** (4 equiv), **2a** (1 equiv), $Cu(OTf)_2$ (10 mol %), bissulfoximine (10 mol %), CH_2Cl_2, −78 °C → rt. [b] Determined by HPLC, using a chiral column (Chiralcel OD). [c] Determined by ^1H NMR spectroscopy. [d] Performed at −50 °C, 48 h.

Table 2. Effect of the Counterion[a]

entry	copper salt	yield (%)	ee (%)[c]	endo/exo
1	$Cu(OTf)_2$	98	75	93:7
2	$CuCl_2$	98	0	93:7
3	$Cu(OOCCF_3)_2$[b]	98	2	90:10
4	$Cu(BF_4)_2$[b]	98	61	88:12
5	$Cu(SbF_6)_2$[b]	98	73	93:7
6	$Cu(PF_6)_2$[b]	98	79	91:9
7	$Cu(ClO_4)_2$[b]	98	86	92:8

[a] Reaction conditions: **1** (4 equiv), **2a** (1 equiv), copper(II) salt (10 mol %), bissulfoximine **5a** (10 mol %), CH_2Cl_2, −78 °C → rt. [b] Prepared in situ from $CuCl_2$ (10 mol %) and AgX (20 mol %). [c] Determined by HPLC, using a chiral column (Chiralcel OD).

(13) With the same catalyst [**4f**, $Cu(OTf)_2$; 10 mol % each] the reaction between **2a** and 1,3-cyclohexadiene gave the corresponding product with 63% ee in 98% yield.

(14) Other metal species such as $Ti(OiPr)_4$, $Sc(OTf)_3$, $Fe(ClO_4)_2$, $Fe(ClO_4)_3$, $Zn(OTf)_2$, $Mg(OTf)_2$, Cu(OTf), $Ag(ClO_4)$, or $Ni(SbF_6)_2$ were also tested and gave products with less than 35% ee

(15) Significant counterion effects have also been observed in reactions with Cu(II)-BOX catalysts (for examples, see refs 10c,d).

75 to 86% ee when changing from $Cu(OTf)_2$ to $Cu(ClO_4)_2$ as the metal source. The endo/exo ratio remained essentially unaffected (entries 1 and 7).

Furthermore, the solvent had a major effect on the enantioselectivity of the product formation (Table 3), even

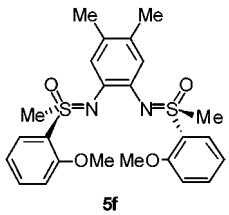
Table 3. Effect of the Solvent[a]

entry	solvent	temp (°C)	ee (%)[b]	endo/exo
1	CH_2Cl_2	−70	75	93:7
2	$CHCl_3$	−60	92	85:15
3	1,1,1-trichlorethane	−30	58	92:8
4	1,2-dichloroethane	−25	67	89:11
5	1,1,2-trichloroethane	−25	80	89:11
6	benzotrifluoride	−25	64	90:10
7	CH_3NO_2	−25	40	91:9
8	THF	−70	15	92:8
9	$(CF_3)_2CHOH$	0	73	89:11

[a] Reaction conditions: **1** (4 equiv), **2a** (1 equiv), $Cu(OTf)_2$ (10 mol %), bissulfoximine **5a** (10 mol %); yields 98%. [b] Determined by HPLC, using a chiral column (Chiralcel OD).

when it was only changed within a relatively narrow range of chlorinated types. Thus, by simply switching from CH_2Cl_2 to $CHCl_3$, the ee of **3a** increased from 75 to 92% in a catalysis by using 10 mol % of $Cu(OTf)_2$ and **5a** as ligand (entries 1 and 2). Unfortunately, the endo/exo ratio was now reduced to 85:15, and the reaction was much slower. Other chlorinated solvents (at slightly higher temperatures) gave **3a** with 58 to 64% ee (entries 3−6). Nitromethane and THF proved unsuitable and provided **3a** with only 40 and 15% ee, respectively (entries 7 and 9). To our surprise, even at 0 °C the catalysis in hexafluoro-2-propanol gave almost the same result as the one performed in CH_2Cl_2 at −70 °C affording **3a** with 73% ee.

From the entire screening process we deduced that an optimal catalytic system for the Diels−Alder reaction between cyclopentadiene (**1**) and acryloyl-2-oxazolidinones **2** catalyzed by copper(II)/bissulfoximine complexes required first, $Cu(ClO_4)_2$ as copper(II) source, second, chloroform as solvent, and third, a novel ligand having an electron-rich bridging arene and methoxy substituents at the ortho-positions of the sulfoximine aryl units. For that purpose, dimethyl-substituted **5f** was synthesized[17] and evaluated in the test reaction.



5f

Pleasingly, we found that our hypothesis was fully confirmed, and that **5f** indeed gave the most enantioselective bissulfoximine copper catalyst for this Diels−Alder reaction so far, leading to **3a** with 93% ee in 98% yield (endo/exo ratio: 89:11) after 48 h at −70 °C.

Under these optimized conditions, the Diels−Alder reaction was then performed with substrates **2b**−**d** as well (Table 4).[18] In the case of **2b** no reaction occurred at −70 °C. At

Table 4. Substrate Scope[a]

entry	product	yield (%)	ee (%)[b]	endo/exo
1	**3a**	98	84	92:8
2	**3b**	97	84	87:13
3	**3c**	94	82	76:24
4	**3d**	0		

[a] Reaction conditions: **1** (4 equiv), **2a-d** (1 equiv), $CuCl_2$ (10 mol %), $AgClO_4$ (20 mol %), bissulfoximine **5f** (10 mol %), $CHCl_3$, room temperature. [b] Determined by HPLC using a chiral column (Chiralcel OD).

room temperature almost full conversion was achieved after 24 h, leading to **3b** with an ee of 84% (endo/exo ratio: 87:13). Acryloyl-2-oxazolidinones **2a** and **2c** afforded **3a** and **3c** with 84% and 82% ee, respectively, at this temperature.[19] The diastereomeric ratios were 92:8 for **3a** and 76:24 for **3c**. A low catalytic activity was observed with **2c** and **2d** as substrates. With the latter, even at 40 °C no reaction took place.

In summary, we demonstrated that various C_2-symmetric bissulfoximines can serve as ligands in copper-catalyzed enantioselective Diels−Alder reactions, and we designed a new system with superior properties. Since the substrate range is still rather limited, further studies are focused on extending the scope of this process, and by ongoing investigations we hope to illustrate the applicability of those new ligands in other asymmetric catalyses.

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Supporting Information Available: Experimental procedures and spectral data for **5a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) We chose to use **5a** in this optimization process, because it is readily available in a one-step process from commercially available starting materials. For details see ref 8.

(17) Bissulfoximines of this type with stronger electron-donating substituents at C4 and C5 have remained inaccessible to date.

(18) For details see the Supporting Information.

(19) In comparison, $[Cu((S,S)$-*t*-Bu-box$)](SbF_6)_2$ affords cycloadducts of type **3** with enantiomeric excesses >94% at ambient temperatures. For details, see: Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582.